Posttraumatic Stress Disorder

Acute and Long-Term Responses to Trauma and Disaster

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Chapter 13

Neurobiological Alterations in PTSD: Review of the Clinical Literature

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Health care professionals generally understand posttraumatic stress disorder (PTSD) as a psychological disorder: in response to extreme stress, an individual develops a host of reexperiencing, avoidance, and hyperarousal symptoms that the person experiences subjectively as psychological or emotional in origin. Therefore, most treatments—including individual psychotherapy, group therapy, pastoral counseling, behavior therapy, and psychoeducation—are nonorganic in nature.

In recent years, psychiatrists increasingly have recognized that they also could consider PTSD from a biological perspective. Since 1980—when DSM-III (American Psychiatric Association 1980) added the term *posttraumatic stress disorder* to the formal nosology—a series of psychophysiological, hormonal, neurotransmitter, receptor binding, electrophysiological, and brain imaging studies have begun to characterize the biological nature of this disorder. These studies strongly support the notion that severe psychological trauma can cause alterations in the patient's neurobiological response to stress, even years after the original insult, and that these longstanding alterations may contribute to a number of complaints and symptoms that patients with PTSD commonly express (Charney et al. 1993; Southwick et al. 1992).

In this chapter, we review clinical studies of neuroendocrine and neurotransmitter alterations in patients with PTSD. Although we

briefly describe preclinical, or animal, studies, we restrict our review primarily to investigations involving humans who have been exposed to trauma. Because most published biological studies have involved combat veterans, our analysis draws heavily on findings from this patient population.

Preclinical studies of stress have repeatedly demonstrated alterations in multiple neuroendocrine systems; nevertheless, human studies largely have been limited to two major neurobiological axes of the stress response: the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. Accordingly, we emphasize these two systems in this chapter, although we mention other systems briefly. Determining the specific behavioral effects of a single neurotransmitter is difficult, if not impossible, because neurotransmitters interact with one another in a complex fashion. Thus, our analysis regarding behavioral correlates of single neurotransmitter system alterations is, by definition, simplistic.

THE SYMPATHETIC NERVOUS SYSTEM

Scientists have long recognized that activation of the SNS plays an important role in an organism's response to stressful or dangerous situations (Cannon 1914). Although functional groups of sympathetic fibers can fire independently, under conditions of extreme stress the system tends to discharge as a unit to maximize mobilization and utilization of energy. Coordinated sympathetic discharge accelerates heart rate and increases blood pressure, allowing for greater perfusion of muscles and vital organs; dilates pupils, so that more light enters the eye; constricts skin vasculature, to limit blood loss should injury occur; shunts blood from temporarily unnecessary splanchnic and renal regions to active muscle groups; and rapidly increases energy supply to skeletal musculature by mobilizing blood glucose and facilitating the oxidation of various food products (Gagnon 1977; Mountcastle 1973). Widespread emergency-stimulated SNS discharge prepares the organism for what Cannon termed the "flight or fight" response (Cannon 1914).

Psychophysiological Studies

Although stress-induced SNS activation serves a protective role in the short run, it may result in long-term negative sequelae for some

individuals. In many individuals who develop PTSD, the SNS appears to become hyperresponsive to a host of trauma-related stimuli. The nature and extent of this hyperresponsiveness has been the subject of intense study.

In 1918, two studies described the first laboratory investigations of SNS activity among traumatized humans. Meakins and Wilson (1918) exposed combat veterans with "shell shock" to the sounds of gunfire and the smell of sulfuric flames; they found that, as a group, these veterans had greater increases in heart rate and respiratory rate than healthy control groups. Fraser and Wilson (1918) demonstrated exaggerated psychophysiological arousal—with marked increases in subjective anxiety, heart rate, and blood pressure—among war veterans, compared with healthy control subjects, in response to intravenous administration of epinephrine.

During World War II, Kardiner coined the term "physioneurosis" to describe a neurosis characterized by hypervigilance, agitation, insomnia, nightmares, and marked physiological arousal, which he believed had a profound underlying biological basis (Kardiner 1941). Grinker and Spiegel (1945) described combat soldiers who behaved as if they had an injection of adrenaline and who suffered from stimulation of the sympathetic nervous system that was chronic in nature. The belief that altered catecholamine function played a critical role in combat neurosis led some clinicians and researchers to advocate bilateral denervation of the adrenal glands as a form of treatment for highly symptomatic war veterans (Crille 1940). The first contemporary psychophysiological study demonstrated that combat sounds caused "decompensated" World War II soldiers to become more behaviorally agitated than World War II soldiers who were not described as decompensated (Dobbs and Wilson 1960).

Since 1980, researchers have conducted a series of psychophysiology studies measuring heart rate, blood pressure, and galvanic skin response at baseline and in response to trauma-related cues (e.g., Blanchard et al. 1982, 1991; Brende 1982; Malloy et al. 1983; Orr 1990; Orr et al. 1993; Pallmeyer et al. 1986; Pitman et al. 1987, 1990a; Shalev et al. 1993). These studies found marked elevations in psychophysiological parameters during provocation but few, if any, differences at baseline between combat veterans and healthy control subjects (for a comprehensive review, see Shalev and Rogel-Fuchs 1993). Researchers did not observe this hyperreactiveness in

combat veterans without PTSD (Pitman et al. 1987) or in combat veterans with anxiety disorders other than PTSD (Pitman et al. 1990a)—suggesting that neither combat exposure alone nor the presence of anxiety disorders other than PTSD is sufficient to explain postwar physiological reactivity. Furthermore, psychophysiological responses to reminders of trauma also are present in civilians with PTSD (Shalev et al. 1993).

Another line of psychophysiological investigation has examined responses to auditory startle. These studies differed somewhat from the foregoing investigations in that they measured response to neutral stimuli (e.g., loud tones, air puffs, visual images) rather than trauma-related stimuli. Shalev and Rogel-Fuchs (1993) suggested that exploration of these responses in PTSD patients, compared with control subjects, would allow researchers to investigate processes that are not confounded by conscious or unconscious behaviors on the part of the subject. Indeed, these studies have provided information about processes such as habituation, learning, and extinction that researchers have hypothesized are relevant to the acquisition of symptoms following trauma and the failure to extinguish responses to reminders of the trauma.

Most of these studies (Butler et al. 1990; Kozak et al. 1988; Paige et al. 1990; Shalev et al. 1993)—although not all (Morgan et al. 1992; Ross et al. 1989)—found abnormalities in habituation in PTSD patients. McFarlane et al. (1993) demonstrated that patients with PTSD failed to differentiate between stimuli of differing relevance; they suggested that their observations were related to disturbed concentration and memory impairments in PTSD and hypothesized that a dysfunction in central noradrenergic systems mediated the observed effect.

Indeed, consistent alterations in psychophysiological responses to stress-related stimuli in humans have prompted researchers to investigate the biochemical underpinnings of SNS activation in traumatized populations. These studies have focused primarily on the three key SNS neurotransmitters: norepinephrine, epinephrine, and dopamine.

Baseline Catecholamine Studies

Twenty-four hour urine studies. Researchers have reported that combat veteran inpatients' mean 24-hour urinary excretion of

norepinephrine is elevated, compared with healthy control subjects (Yehuda et al. 1992) and psychiatric patients (Kosten et al. 1987). Pitman and Orr (1990) reported that the mean norepinephrine level in combat veterans without PTSD was statistically equivalent to that in combat veterans with PTSD, suggesting that alterations in norepinephrine excretion may be a function of trauma rather than PTSD per se. Indeed, the mean norepinephrine excretion in both groups was comparable with the level that Yehuda et al. (1992) observed for combat veterans with PTSD. Furthermore, L.M. Davidson and Baum (1986) reported elevations in resting heart rate, blood pressure, and urinary norepinephrine in residents living within 5 miles of the Three Mile Island nuclear power plant, regardless of PTSD status.

Studies of urinary epinephrine have produced less consistent results. Although Kosten et al. (1987) and Yehuda et al. (1992) reported increased levels of 24-hour urinary epinephrine excretion among inpatients with PTSD, outpatients with PTSD did not appear to have higher epinephrine excretion (Pitman and Orr 1990; Yehuda et al. 1992). Urinary dopamine excretion, however, was elevated in inpatients with PTSD and in outpatients with PTSD (Yehuda et al. 1992).

Baseline plasma studies. Unlike 24-hour urine studies, baseline plasma norepinephrine studies generally have found no significant differences between PTSD patients and healthy control subjects. In separate studies measuring norepinephrine responses to war-related laboratory stimuli, McFall et al. (1990) and Blanchard et al. (1991) reported similar resting baseline norepinephrine values in PTSD patients and control subjects; McFall et al. (1990) also found no differences in baseline levels of plasma epinephrine. Hamner et al. (1994) measured noradrenergic responsiveness in combat veterans with PTSD following exercise stress; they also found no baseline differences between patients and control subjects. Finally, Southwick et al. (1993a) reported comparable baseline plasma levels of the major norepinephrine metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), prior to yohimbine infusion among PTSD patients and control subjects.

However, the only published study examining plasma levels of dopamine (Hamner et al. 1990) suggested that resting levels of that

neurotransmitter may be higher in PTSD patients than in control subjects. This finding is compatible with observations of increased urinary dopamine excretion (Yehuda et al. 1992).

Receptor studies. α_2-Adrenergic receptors play a key role in translating the neurochemical message of norepinephrine and epinephrine. As such, the functional status of the α_2 receptor may provide information about the long-term effects of alterations in catecholamine neurotransmission. Two separate radioligand-binding studies—one involving combat veterans (Perry et al. 1987) and another involving traumatized children (Perry 1994)—found fewer total α_2-adrenergic receptor binding sites per platelet in subjects with PTSD than in control subjects. Perry et al. (1990) hypothesized that chronic elevation of circulating catecholamines likely causes a "downregulation" or reduced number of available receptor sites. This reduction in the number of available receptor sites may represent an adaptive response to overstimulation by the agonist.

Using an in vitro model, Perry et al. (1990) also found that high concentrations of epinephrine caused a rapid and extensive loss of receptor protein from the platelet membranes of two PTSD patients compared with two control subjects. This preliminary finding appears to be consistent with a receptor-effector system that has been taxed by excessive exposure to the agonist and becomes easily fatigued.

Lerer et al. (1987, 1990) examined adenylate cyclase activation in platelet membranes, as well as cyclic adenosine monophosphate (cAMP) signal transduction in platelet membranes and intact lymphocytes, of PTSD patients. In lymphocyte preparations, basal cAMP levels and responsiveness to isoproterenol and forskolin stimulation was lower in PTSD patients than in control subjects. These findings appear to reflect diminished responsiveness of the receptor adenylate-cyclase complex in patients with PTSD. The results of the studies by Lerer et al. (1987, 1990) and Perry et al. (1990) point to potential abnormalities at the adrenergic receptor level and at sites distal to the receptor; these findings require further clarification.

Provocation or Challenge Studies

Challenge studies are designed to evaluate biological systems under controlled conditions that intentionally provoke the system.

Under this approach, the researcher exposes the subject to external stimuli such as recorded trauma transcripts or exogenously administered biological substances, then records behavioral, physiological, and neuroendocrine responses to the provocation. The results allow the researcher to draw inferences about the functional status of the particular biological system under investigation.

McFall et al. (1990) found parallel increases and higher levels of subjective distress, blood pressure, heart rate, and plasma epinephrine in combat veterans with PTSD than in control subjects during and after a combat film but not in response to the film of an automobile accident. The parallel increases suggested that heightened physiological reactivity was related to circulating catecholamines—specifically, epinephrine—and that the heightened response was specific to trauma-related cues. Blanchard et al. (1991) reported similar changes in norepinephrine using auditory combat-related stimuli; their comparison group comprised combat veterans without PTSD.

Dinan et al. (1990) used a desipramine growth hormone challenge to probe postsynaptic α_2-adrenergic receptor function in 8 traumatized women; they found no difference between traumatized subjects with PTSD and control subjects in desipramine-stimulated growth hormone levels. Using an intravenous challenge paradigm in a 20-year-old car accident victim with PTSD, Hansenne et al. (1991) reported a blunted growth hormone response to intravenous clonidine. Researchers generally believe that the growth hormone response to clonidine is an index of noradrenergic function; blunting therefore suggests heightened noradrenergic sensitivity, along with possible downregulation of noradrenergic receptors. After successful treatment, Hansenne et al. (1991) reported a normal growth hormone response to clonidine, which they interpreted as evidence for a relationship between noradrenergic dysregulation and PTSD-specific symptoms.

Intravenous lactate infusion causes panic attacks in patients with panic disorder. Although the precise mechanism of lactate-induced anxiety and panic is unknown, researchers have suggested central noradrenergic stimulation. In a study of seven Vietnam veterans with PTSD, Rainey et al. (1987) reported panic attacks in six of the seven subjects and flashbacks in all seven; because the subjects who had lactate-induced panic attacks also met criteria for comorbid panic disorder, however, the investigators could not determine whether the responses were secondary to panic disorder, PTSD, or both.

Yohimbine offers a more direct probe of noradrenergic activity. Yohimbine is an α_2-adrenergic receptor antagonist that activates noradrenergic neurons by blocking the α_2-adrenergic autoreceptor, thereby increasing presynaptic noradrenergic release. Southwick et al. (1993a) compared responses to yohimbine in 20 Vietnam combat veterans with those in 18 control subjects. Although yohimbine acts on multiple neurotransmitter systems, at the dose employed by Southwick et al. (1993a) it primarily affects the noradrenergic system. Yohimbine produced panic attacks in 70% of patients with PTSD and flashbacks in 40% of PTSD patients; there were no yohimbine-induced panic attacks or flashbacks among the control group. Plasma MHPG following yohimbine administration was elevated more than twice as much in patients with PTSD compared with control subjects—suggesting abnormal presynaptic noradrenergic reactivity in PTSD patients.

Yohimbine did not produce similar effects in major depressive disorder, schizophrenia, obsessive-compulsive disorder, or even generalized anxiety disorder (Charney et al. 1990). Yet, it resulted in comparable behavioral and cardiovascular responses in panic disorder patients (Charney et al. 1987), suggesting that PTSD and panic disorder share a common neurobiological abnormality that is related to altered sensitivity of the noradrenergic system. Because 43% of the patients with PTSD in the Southwick et al. (1993a) study did not meet criteria for comorbid panic disorder, the presence of panic disorder could not by itself explain yohimbine-induced panic attacks. Yet 89% of patients meeting criteria for both PTSD and panic disorder had yohimbine-induced panic attacks. Comorbid panic disorder in patients with PTSD may simply reflect a more pronounced abnormality of the noradrenergic system.

In summary, baseline or resting studies generally have found no differences in plasma catecholamine levels between combat veterans with PTSD and healthy control subjects. However, most 24-hour urine studies have reported increased excretion of catecholamines, and most challenge studies have found evidence for hypersensitivity of the noradrenergic system. Although 24-hour urine studies do not involve direct laboratory provocation, they do incorporate hormonal responses to day-to-day stressors. That is, catecholamine levels in 24-hour urine samples reflect the summation of phasic

physiological changes in response to meaningful stimuli, as well as tonic resting levels of autonomic arousal (Murburg 1994).

The studies reviewed earlier point to increased responsiveness of the SNS that is detectable under conditions of stress in severely traumatized individuals with PTSD. These findings are consistent with data showing consistent elevations in psychophysiological reactivity to trauma-related cues in combat veterans with PTSD. Researchers have not found conclusive psychophysiological evidence of tonic or baseline elevations, however.

THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Selye (1956) proposed the general adaptation syndrome as an extension of Cannon's flight-or-fight response (Cannon 1914). Studies of the general adaptation syndrome focused on the pituitary-adrenocortical response to stress. In response to stress, neuropeptides and neuromodulators stimulate the release of corticotropin releasing factor (CRF), which in turn stimulates the adrenal gland to release cortisol. Selye hypothesized that the amount of cortisol released during stress provides an index of stressor severity; Mason (1968) and Mason et al. (1976) provided clear evidence for a linear relationship between cortisol release and stressor severity.

Studies of the HPA axis in PTSD, however, have provided data that are incompatible with Selye's notion of the stress response (Yehuda et al. 1993b). For example, rather than the increased cortisol levels that the theory of general adaptation might predict, PTSD patients show evidence of low cortisol levels and other HPA-axis abnormalities that suggest a heightened sensitivity of this axis to stress.

Baseline Studies

Several studies have replicated the finding of low urinary cortisol excretion in patients with PTSD compared with other psychiatric patients and healthy control subjects. Mason et al. (1986) observed lower mean 24-hour urinary cortisol excretion in nine PTSD patients than in patients in four other diagnostic groups. Similarly, Yehuda et al. (1993a) found low urinary cortisol in PTSD, compared with major depression, panic disorder, bipolar mania, and schizophrenia. Urinary cortisol excretion also was lower in inpatient and outpatient combat

veterans with PTSD than in nonpsychiatric, healthy control subjects (Yehuda et al. 1990). Low urinary cortisol levels do not appear to be solely a function of exposure to trauma: Yehuda et al. (1993b, 1995) found low urinary cortisol levels in Holocaust survivors with PTSD, but not Holocaust survivors without PTSD, compared with demographically matched healthy subjects. The only other study examining 24-hour urinary cortisol excretion (Pitman and Orr 1990) reported increased urinary cortisol levels in PTSD patients; this study differed, however, in the method of urine collection, radioimmunoassay, and other variables (see Yehuda et al. 1991a).

A recent study examining the circadian release of cortisol over the 24-hour diurnal cycle further supports the theory that basal plasma cortisol release is significantly lower in patients with PTSD than patients with major depression and healthy control subjects. Yehuda et al. (in press) found that cortisol levels were significantly lower—primarily in the late evening and early morning hours—in patients with PTSD. Chronobiological analysis of raw cortisol levels using multioscillator cosinor modeling revealed a higher "signal-to-noise" ratio of cortisol release in subjects with PTSD. That is, relative to lower cortisol excretion, PTSD patients tended to show large cortisol fluctuations. The investigators interpreted these data as reflecting a more dynamic HPA axis in PTSD.

Lymphocyte glucocorticoid receptors. Because hormones cannot exert their genomic effects unless they are bound to steroid receptors, researchers have suggested that steroid receptor binding parameters are important in interpreting studies examining basal hormone secretion. Furthermore, because lymphocytes and brain glucocorticoid receptors share similar regulatory and binding characteristics, researchers also have suggested that lymphocyte glucocorticoid receptor function reflects aspects of peripheral and central cortisol regulation (Lowy 1989; Lowy et al. 1985).

Yehuda et al. (1991b, 1993a, in press) found higher numbers of lymphocyte glucocorticoid receptors in combat veterans with PTSD than in nonpsychiatric and psychiatric comparison groups. These findings are consistent with observations of low cortisol in PTSD; low circulating levels of a hormone or neurotransmitter usually are associated with an upregulation or increased number of receptors.

Yehuda (in press) also reported that glucocorticoid receptor numbers appeared to be significantly higher in combat veterans without PTSD than in healthy control subjects. This finding suggests that trauma exposure per se may result in long-lasting changes in glucocorticoid receptors. Yet, the number of glucocorticoid receptors in combat veterans who do not meet DSM-IV diagnostic criteria for PTSD appears to be smaller than the number in combat veterans with PTSD. Future studies exploring associations among trauma exposure severity, PTSD symptoms, and glucocorticoid receptor numbers are necessary to address definitively the cause of glucocorticoid receptor alterations in persons exposed to trauma.

Provocation or Challenge Studies

Researchers have used two HPA-axis challenge paradigms to study PTSD: the dexamethasone suppression test (DST) and the corticotropin releasing factor (CRF) test. Both tests provide information about central nervous system mechanisms involved in the regulation of glucocorticoids.

DST studies. Dexamethasone is a synthetic glucocorticoid that mimics the effect of cortisol; it directly inhibits the release of CRF and adrenocorticotropic hormone (ACTH). The DST involves administration of 1 mg dexamethasone at 11:00 A.M., when normal cortisol secretion is at its nadir in the diurnal cycle. The inhibition of CRF and ACTH results in a decrease in the amount of cortisol released from the adrenal gland. Administration of dexamethasone substantially reduces cortisol secretion in healthy individuals within hours; a 1-mg dose normally suppresses plasma cortisol to a level below 5 μg/dl at 8:00 A.M., and cortisol usually remains at that level at 4:00 A.M.

Studies examining cortisol response to dexamethasone in psychiatric disorders, most notably major depressive disorder, have repeatedly found nonsuppression of cortisol in about 40%–60% of depressed patients (for a comprehensive review, see APA Task Force 1987; Carroll 1982; Carroll et al. 1981). This nonsuppression likely results from either a reduced ability of glucocorticoids to suppress the release of CRF and ACTH or adrenal cortisol hypersecretion.

Five studies have investigated cortisol response to 1 mg of dexamethasone in patients with PTSD; all reported that PTSD patients without major depression had a "normal" suppression response (Dinan et al. 1990; Halbreich et al. 1989; Kosten et al. 1990; Kudler et al. 1987; Olivera and Fero 1990). Closer examination, however, revealed that PTSD patients as a group showed an exaggerated response to dexamethasone. Yehuda et al. (1991a) conducted a meta-analysis of research on the DST in PTSD patients. They averaged the mean cortisol data across all published studies; this calculation revealed a cortisol value in nondepressed PTSD subjects of 1.74 μg/dl—a value well below the established normal threshold of 5.0 μg/dl.

Findings of cortisol suppression following administration of dexamethasone in PTSD patients with major depression are less clear. Kudler et al. (1987), for example, reported that PTSD patients with major depressive disorder showed a rate of nonsuppression comparable with the rate observed in patients with major depressive disorder without PTSD, whereas Halbreich et al. (1989) and Kosten et al. (1990) found normal responses to dexamethasone even in depressed combat veterans with PTSD.

Olivera and Fero (1990) reported a 32% rate of nonsuppression in 65 combat veterans with PTSD who met comorbid criteria for major depressive disorder, although these individuals showed normal suppression after their major depression had remitted. A study examining cortisol response to dexamethasone in eight civilian women with PTSD (Dinan et al. 1990) also found normal responses to dexamethasone. The mean 4:00 P.M. postdexamethasone cortisol values of the 73 PTSD patients with comorbid depression in these two studies were somewhat higher than those reported for PTSD patients without major depression, although still well below the 5.0 μg/dl threshold for major depression.

Most of the DST studies in PTSD patients were conducted before researchers appreciated that cortisol levels in these patients tended to be lower and the number of glucocorticoid receptors larger than in healthy subjects. Therefore, these studies were designed to test for nonsuppression in PTSD; they did not focus on the possibility of an exaggerated cortisol response, or hypersuppression, to dexamethasone. Failure to observe the classic nonsuppression response to

cortisol, coupled with reported HPA-axis alterations that appeared distinct from those in depression, prompted investigators to conduct studies designed to detect potential enhanced suppression of the cortisol response to dexamethasone.

Two studies explored the issue of enhanced cortisol suppression to dexamethasone, using 0.50-mg (Yehuda et al. 1993c) and 0.25-mg (Yehuda et al. in press) doses of dexamethasone. These studies found hyperresponsiveness to low doses of dexamethasone—as reflected by significantly lower cortisol levels—in PTSD patients compared with healthy subjects. Downregulation of cytosolic lymphocyte glucocorticoid receptors accompanied enhanced suppression of cortisol (Yehuda et al. in press). Interestingly, investigators found hyperresponsiveness to dexamethasone in combat veterans with PTSD who met the diagnostic criteria for major depressive disorder (Yehuda et al. 1993c) but not in combat veterans without PTSD (Yehuda et al. in press).

Hypersuppression of cortisol following administration of dexamethasone suggests that patients with PTSD do not exhibit a "classic" stress response as defined by Selye (1956). Furthermore, researchers have not observed this hypersuppression in other psychiatric disorders; it may serve as a relatively specific marker for PTSD.

CRF studies. The CRF challenge test measures the pituitary ACTH and adrenal cortisol response to exogenous infusion of the neuropeptide CRF. Investigators have demonstrated attenuation of the normal ACTH response to CRF in patients with major depressive disorder (Gold et al. 1985, 1986; Holsboer et al. 1985, 1986). This blunted ACTH response typically occurs in hypercortisolemic patients; researchers believe this response reflects a decreased number of pituitary CRF receptors, caused by hypothalamic CRF hypersecretion (Gold et al. 1986; Holsboer et al. 1986), and/or increased negative feedback inhibition of the pituitary secondary to abnormally high circulating cortisol levels (Lowy et al. 1985).

A single study of eight subjects with PTSD suggested that the ACTH response to CRF also was blunted (Smith et al. 1989). The attenuated ACTH response in PTSD patients, however, occurred in the presence of normal, not elevated, evening plasma cortisol levels. Thus, the response to CRF in patients with PTSD may reflect

a decreased pituitary sensitivity to CRF or an enhanced effect of glucocorticoid negative feedback on the pituitary, rather than a decrease in the number of CRF receptors (which researchers believe occurs in major depression).

OTHER NEUROBIOLOGICAL SYSTEMS

Animal studies of stress support the notion that multiple neurochemical systems can become altered in animals that have been exposed to traumatic, uncontrollable stressors (Southwick et al. 1992). In human studies, researchers have reported changes in opiate, serotonin, γ-aminobutyric acid (GABA), dopamine, and other hormone systems, in addition to catecholamine and HPA-axis alterations.

Opiates

Uncontrollable stress causes an increase in endogenous opiate release and a subsequent increase in analgesia (Amir et al. 1986; Hemingway and Reigle 1987; Pitman et al. 1990b). Particularly after injury, this increase in analgesia appears to be adaptive, allowing the organism to focus its attention on behaviors that are necessary for survival. In animal and human studies, administration of the opiate antagonist nalaxone blocked stress-induced analgesia (Jackson et al. 1979; Maier 1986; Pitman et al. 1990b). Using combat films as stressors, Pitman et al. (1990b) found that stress-induced analgesia appeared to be significantly greater among combat veterans with PTSD than among healthy control subjects, suggesting that the endogenous opiate system may be involved in the pathophysiology of PTSD.

Serotonin

Preclinical studies examining the response of serotonin systems to traumatic stress have produced mixed results (see Charney et al. 1993). In humans, however, serotonin appears to play an important role in the regulation of aggression, impulsivity, and mood (Yehuda et al. 1988). Aberrations in these affects and behaviors are common in traumatized individuals with PTSD, suggesting that alterations

in serotonin regulation may play a role in PTSD symptom formation.

Arora et al. (1993) reported a significant decrease in platelet 5-HT uptake among PTSD patients compared with healthy subjects and PTSD patients meeting criteria for comorbid major depression. Furthermore, mCPP (a mixed 5-HT receptor agonist) appears capable of inducing flashbacks and panic attacks in a subgroup of combat veterans with PTSD, suggesting heightened sensitivity of serotonergic receptors in this subpopulation (Southwick et al., unpublished data). Evidence of the partial efficacy of serotonin re-uptake inhibitors in treating PTSD-specific symptoms (J.R.T. Davidson et al. 1991; McDougal et al. 1991; Nagy et al. 1993; Shay 1992) further supports serotonergic involvement.

Thyroid

Kosten et al. (1990) compared the thyroid-stimulating response (TSR) to thyroid-releasing hormone (TRH) in 11 PTSD patients with the TSR in 28 depressed patients. In contrast to the classic blunted TSR response exhibited by many depressed patients, four of the 11 PTSD patients showed an augmented response to TRH. Mason et al. (1989) reported elevated thyroid levels in patients with PTSD compared with patients in several other diagnostic groups. More recently, Mason et al. 1994 found elevations of serum total triiodothyronine (T3) in a sample of combat veterans with PTSD (N = 96); they also observed increased levels of free T3, total thyroxine (T4), and thyroid-binding globuine (TBG). Free T4 levels were not elevated, suggesting that PTSD may involve increased peripheral conversion of T4 to T3 and increased thyroid hormone binding. The authors hypothesized that disturbances in the noradrenergic system underlie these thyroid disturbances.

Testosterone

Mason et al. (1990) found substantially higher serum testosterone concentrations in patients with PTSD than in patients with major depressive disorder, patients with bipolar disorder, and healthy subjects; testosterone levels in PTSD patients were comparable with those in schizophrenic patients. Although the clinical characteristics of these

findings must be explored, the data lend further support to the neuroendocrine distinctiveness of PTSD and major depressive disorder.

SUMMARY

The studies we have reviewed in this chapter provide evidence for at least two relatively consistent neurobiological alterations in chronic PTSD. First, findings from psychophysiological, hormonal, receptor binding, and intravenous challenge studies have demonstrated repeatedly that reminders of the original trauma provoke hyperresponsiveness of the SNS in patients with PTSD (although studies of resting or baseline SNS activity have shown no consistent differences between patients with PTSD and control subjects). Researchers have examined a variety of parameters of altered SNS hypersensitivity, including blood pressure, pulse, plasma and urine norepinephrine and epinephrine, and plasma MHPG. Second, findings of HPA-axis alterations in PTSD suggest increased responsiveness of this system as well. Low baseline cortisol, coupled with heightened response to exogenous dexamethasone, is consistent with an HPA axis that is extremely sensitive to stress hormones. A recent chronobiological analysis of diurnal cortisol metabolism supports a mathematically derived model of enhanced signal-to-noise in the HPA axis among combat veterans with PTSD; this analysis offers further evidence of increased sensitivity.

These findings are consistent with a behavioral sensitization model of PTSD. Behavioral sensitization refers to an increased magnitude of response following repeated presentations of a particular stimulus. In this paradigm, following a stressful event, physiologic, biochemical, and behavioral responses to subsequent stressors increase over time. For example, dopamine-hydroxylase activity, tyrosine hydroxylase, and synaptic levels of norepinephrine all increase in animals exposed to repeated shock (Irwin et al. 1986; Karmarcy et al. 1984; Melia et al. 1991). When these repeatedly shocked animals subsequently are exposed to a limited shock, they respond as if the shock were much greater, by releasing an amount of norepinephrine that is appropriate for a much larger stressor. Over time, therefore, repetitive stress appears to cause a compensatory increase in norepinephrine synthesis and subsequent release.

Laboratory-induced behavioral sensitization and PTSD exhibit a number of parallels. In both cases, prior exposure to stressors may increase subsequent responses to stressors depending on variables such as dose, as well as frequency and intermittency of exposure (Antelman 1988; Post 1992; Post and Contel 1983). Animals that receive a large initial dose of cocaine, for example, show greater response on reexposure than animals that receive a small initial dose (Weiss et al. 1989). Similarly, in traumatized humans, the magnitude of combat exposure is positively correlated with the development of PTSD (Kulka et al. 1990; Southwick et al. 1993b), and prior exposure to childhood trauma—particularly trauma that is repetitive in nature—may increase the likelihood of PTSD symptoms (Bremner et al. 1993; Putnam 1993). A study of Israeli combat soldiers who fought in two successive wars, for example, found that soldiers were more likely to develop symptoms during the second war if they had suffered acute combat stress during the first war (Solomon et al. 1987).

For many patients with PTSD, symptoms do not diminish over time; instead, they increase in magnitude. Archibald and Tuddenham (1965) studied World War II veterans 20 years after the war; patients with PTSD reported increases in symptoms with the passage of time. Similarly, animal studies of behavioral sensitization and "time dependent change" (Antelman and Yehuda 1994) show that stressors can cause long-lasting and gradually increasing changes in behavioral and physiological responses to subsequent stressors.

Some researchers have advanced other neurobiological models to explain certain aspects of PTSD. These alternative paradigms include fear conditioning (Davis 1986; LeDoux 1990), overconsolidation of memory (McGaugh 1990; Pitman 1989), and failure of extinction (LeDoux 1990; Shalev and Rogel-Fuchs 1993).

Fear conditioning refers to the pairing or association of a wide variety of neutral stimuli that are present at the time of a trauma with feelings of terror and extreme anxiety evoked by the trauma (Davis 1986; LeDoux 1990). Fear conditioning causes these previously neutral stimuli to evoke similar feelings of terror. For example, the smell of burning firewood—a neutral stimulus—can act as a conditioned stimulus for an individual who has lived through a life-threatening fire. After the life-threatening fire, the smell of burning wood no

longer elicits feelings of comfort and peace; instead, it evokes fear and terror. Kolb and Multalipassi (1982) termed this association the "conditioned emotional response."

Overconsolidation of memory is a process that is relatively indelible in nature; it may be established via thalamo-amygdala pathways during states of high emotion, such as fear or danger. Researchers have postulated that multiple neuromodulators—including norepinephrine, epinephrine, and opioid peptides—released in high concentrations during situations of fear contribute to overconsolidation of memory, which subsequently causes patients to reexperience symptoms such as flashbacks and nightmares (Pitman 1989). Alternatively, increased neuromodulator release at the time of the trauma may be related to the subsequent distress individuals feel when they are reminded of the original trauma.

Conditioned emotional responses usually diminish in intensity following repeated presentations of fear-conditioned stimuli, in the absence of traumatic stimuli. Researchers have suggested that the intransigence of PTSD symptomatology relates to a failure to extinguish conditioned emotional responses. *Failure of extinction* refers to a potential deficit in neuromechanisms involved in response reduction following repeated presentations of a fear-conditioned stimulus in the absence of a contiguous traumatic event (Charney et al. 1993).

Researchers have not demonstrated the applicability of such animal models of stress to PTSD (Yehuda and Antelman 1993). Although empirical research with human subjects has not yet established how these paradigms relate to PTSD, such models may be useful heuristic tools for understanding discrete aspects of human responses to trauma.

CONCLUSION

The foregoing review suggests that some aspects of PTSD are neurobiologically mediated, at least in part. In this chapter, we highlight recent advances in psychophysiological, hormone, and receptor assay methodology. As methodology in areas such as brain scanning becomes increasingly refined, researchers soon may be able to delineate more accurately the acute and long-term stress-induced changes in central and peripheral nervous system functioning. Clearer

understanding of biological pathophysiology should enable psychiatrists to develop more specific and effective treatments for PTSD.

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